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AU 1646

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- MPI Other

PTO-1590 (9-90)

mertz3

> s (interleukin-1 or IL-1)

```
          3912 INTERLEUKIN
       2256152 1
          1440 INTERLEUKIN-1
                 (INTERLEUKIN(W)1)
         11014 IL
       2256152 1
          1880 IL-1
                 (IL(W)1)
L4        2436 (INTERLEUKIN-1 OR IL-1)
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=> s l4 (5a) (antagonis?)

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         17200 ANTAGONIS?
L5         135 L4 (5A) (ANTAGONIS?)
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=> s l4 (5a) (antagonist?)

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         15344 ANTAGONIST?
L6         133 L4 (5A) (ANTAGONIST?)
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=> s l6 (5a) (DNA or polynucleotide? or nucleotide?)

```
         22723 DNA
          4896 POLYNUCLEOTIDE?
         13325 NUCLEOTIDE?
L7           3 L6 (5A) (DNA OR POLYNUCLEOTIDE? OR NUCLEOTIDE?)
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=> d l7 1-3 cit ab

1. 5,714,140, Feb. 3, 1998, Method for inhibiting the production of bioactive IL-1 by administering M-CSF; Gideon Strassmann, 424/85.1; 514/2, 8, 12, 885; 530/351 [IMAGE AVAILABLE]

US PAT NO: 5,714,140 [IMAGE AVAILABLE] L7: 1 of 3

ABSTRACT:
This invention provides medical uses of a M-CSF, particularly a method and composition for treating inflammatory disease and allergy using natural M-CSF or recombinant M-CSF or the derivatives thereof.

2. 5,698,399, Dec. 16, 1997, Detecting genetic predisposition for osteoporosis; Gordon W. Duff, et al., 435/6, 91.2 [IMAGE AVAILABLE]

US PAT NO: 5,698,399 [IMAGE AVAILABLE] L7: 2 of 3

ABSTRACT:
The present invention relates to methods of predicting the risk of osteoporosis. Specifically, the methods comprise isolating genomic DNA from an individual and determining an allelic pattern for **IL-1** receptor **antagonist** (IL-1ra) in the genomic **DNA**. The identification of at least one copy of allele 2 indicates increased susceptibility to osteoporosis.

3. 5,334,380, Aug. 2, 1994, Anti-endotoxin, interleukin-1 receptor antagonist and anti-tumor necrosis factor antibody with arginine-free formulations for the treatment of hypotension; Robert G. Kilbourn, et

al., 424/85.2, 145.1, 150.1, 158.1, 164.1; 426/656; 514/12, 21 [IMAGE AVAILABLE]

US PAT NO: 5,334,380 [IMAGE AVAILABLE] L7: 3 of 3

ABSTRACT:
Methods and compositions for treating and inhibiting hypotension related to both endotoxin and cytokine-induced shock are provided. A therapeutic regimen useful in the present invention includes an arginine-free parenteral formulation administered with or followed by the administration of an anti-endotoxin antibody, an interleukin-1 or interleukin-2 receptor antagonist, an anti-tumor necrosis factor antibody or a combination thereof. Most preferably, the administration of an arginine-free parenteral formulation augments the anti-hypotensive effect of the various antibodies and antagonist described so as to provide an effective treatment for various forms of hypotension. The therapeutic regimens of the invention are proposed to provide for a decrease in nitric oxide synthase, and thereby an increase in blood pressure in vivo, particularly in animals with cytokine- and/or endotoxin-induced hypotension. The parenteral formulation of the therapeutic regimen and methods of the invention are arginine-free and provide a decrease in plasma arginine levels. Reduced plasma, serum, or tissue levels of arginine in the animal function to augment the hypertensive action of the various antibodies and antagonist to be administered concurrently or subsequent to the administration of the parenteral formulation. Limiting and/or eliminating substrate arginine for nitric oxide synthesis, coupled with limiting and/or eliminating induction of nitric oxide synthase activity with the antibodies and antagonists of the present invention, provides a regimen for treating and/or inhibiting hypotension attendant a variety of conditions and treatments, including chemotherapeutic agent therapy (IFN, TNF, IL-1, IL-2), septic shock, trauma, exposure to endotoxins or cytokines, or other conditions in which hypotension is attendant.

=> s (interleukin-1 receptor?)

L5 3125 (INTERLEUKIN-1 RECEPTOR?)

=> s l5 (5a) (antagonist?)

L6 2113 L5 (5A) (ANTAGONIST?)

=> s l6 (5a) (DNA or nucleotide? or polynucleotide?)

L7 17 L6 (5A) (DNA OR NUCLEOTIDE? OR POLYNUCLEOTIDE?)

=> d l7 1-17 bib ab

L7 ANSWER 1 OF 17 MEDLINE
AN 1998077334 MEDLINE
DN 98077334
TI Effects of recombinant human osteogenic protein 1 on the production of proteoglycan, prostaglandin E2, and interleukin-1 receptor antagonist by human articular chondrocytes cultured in the presence of interleukin-1beta.
AU Huch K; Wilbrink B; Flechtenmacher J; Koepp H E; Aydelotte M B; Sampath T K; Kuettner K E; Mollenhauer J; Thonar E J
CS Rush Medical College at Rush-Presbyterian-St. Luke's Medical Center, Chicago, Illinois 60612, USA.
NC 2-P50-AR39239 (NIAMS)
AG-04736 (NIA)
SO ARTHRITIS AND RHEUMATISM, (1997 Dec) 40 (12) 2157-61.
Journal code: 90M. ISSN: 0004-3591.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 199803
EW 19980303
AB OBJECTIVE. Recombinant human osteogenic protein 1 (OP-1) is an effective stimulator of human cartilage 35S-proteoglycan synthesis. The present study was conducted to determine whether stimulation of human articular chondrocytes with OP-1 can help overcome interleukin-1beta (IL-1beta)-induced suppression of 35S-proteoglycan synthesis. METHODS. Human articular chondrocytes in alginate beads were maintained for 3 days in the absence (control) or presence of IL-1beta at 0.1-100 pg/ml with or without OP-1 at 50 ng/ml, in medium containing 10% fetal bovine serum (FBS). Incorporation of 35S-sulfate into proteoglycans was quantified during the last 4 hours of culture and reported as counts per minute per microg ***DNA***. Release of ***interleukin*** - ***1*** ***receptor*** ***antagonist*** (IL-1Ra) and prostaglandin E2 into the medium was monitored by immunoassay. RESULTS. IL-1beta at 10 pg/ml caused a 60% decrease in 35S-proteoglycan synthesis. This could be blocked by including 500 ng/ml IL-1Ra in the medium. The presence of 50 ng/ml OP-1 in the IL-1beta-containing medium was effective in restoring 35S-proteoglycan synthesis to the level of that found in cultures not treated with IL-1beta. The restorative effects of OP-1 and IL-1Ra were cumulative. The rate of release of prostaglandin E2 and IL-1Ra into the medium was not affected by the presence of OP-1. CONCLUSION. Treatment of human articular chondrocytes with OP-1 cultured in the presence of FBS is effective in overcoming the down-regulation of proteoglycan synthesis induced by low doses of IL-1beta.

L7 ANSWER 2 OF 17 MEDLINE
AN 97331720 MEDLINE
DN 97331720
TI Perifollicular transgenic expression of human interleukin-1 receptor antagonist protein following topical application of novel liposome-plasmid DNA formulations in vivo.
AU Niemiec S M; Latta J M; Ramachandran C; Weiner N D; Roessler B J
CS College of Pharmacy, University of Michigan, Ann Arbor 48109-1065, USA.
SO JOURNAL OF PHARMACEUTICAL SCIENCES, (1997 Jun) 86 (6) 701-8.
Journal code: JO7. ISSN: 0022-3549.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199709
EW 19970904
AB Expression plasmid ***DNA*** for the human ***interleukin*** - ***1*** ***receptor*** ***antagonist*** (IL-1ra) protein was formulated with nonionic:cationic (NC) liposomes or phosphatidylcholine:cationic (PC) liposomes and applied to the auricular skin of hamsters in single- and multiple-dose protocols. Confocal microscopy identified delivery of plasmid DNA proximal to perifollicular cells, and successful transfection of perifollicular cells was identified by immunohistochemistry and ELISA. Skin treated for 3 days with the NC liposomes had statistically significant levels of transgenic IL-1ra present for 5 days post-treatment. Expression of transgenic IL-1ra was specific to areas of skin treated with NC liposomes but not PC liposomes. The results indicate that the NC liposomes can deliver expression plasmid DNA to perifollicular cells and mediate transient transfection in vivo.

L7 ANSWER 3 OF 17 MEDLINE
AN 97304194 MEDLINE
DN 97304194
TI Transfer of genes to chondrocytic cells of the lumbar spine. Proposal for a treatment strategy of spinal disorders by local gene therapy.
AU Wehling P; Schulitz K P; Robbins P D; Evans C H; Reinecke J A
CS Praxis und Klinik fur Orthopadie und Neurochirurgie, Dusseldorf, Germany.
SO SPINE, (1997 May 15) 22 (10) 1092-7.
Journal code: UXK. ISSN: 0362-2436.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199710
EW 19971001
AB STUDY DESIGN: In the current study, chondrocytic cells from bovine intervertebral end plates were cultivated in vitro and modified genetically. OBJECTIVE: The authors intended to perform isolation and cultivation of cells from bovine end plates of the spine. They also intended to show, in principle, the feasibility of introducing exogenous genes into chondrocytic cells from bovine intervertebral end plates by way of retroviral vectors. SUMMARY OF BACKGROUND DATA: The involvement of cytokines in the destruction of articular cartilage is established. It appears possible that similar mechanisms may play a role in intervertebral disc degeneration and other spinal disorders. Conventional medication and surgery of intervertebral disc degeneration addresses neither the pathophysiology nor the chronicity of the disease. Therapeutic proteins carry great potential as locally produced drugs after transfer of their cognate genes to the sites of interest. METHODS: Vertebral end plate tissue was obtained from bovine os coccygis. Chondrocytic cells were isolated and cultured in vitro. The bacterial beta-galactosidase (LacZ) gene and, alternatively, the complementary DNA (DNA copy of the mRNA) of the human interleukin-1 receptor antagonist were introduced into the isolated cells by retrovirus mediated gene transfer. beta-galactosidase activity was determined by staining, and interleukin-1 receptor antagonist protein was quantitated by enzyme-linked immunosorbent assay. RESULTS: Isolation and cultivation of chondrocytic end plate cells is possible. Native cells continue to grow in culture for more than 2 months. Transfer of the beta-galactosidase gene to cultured cells resulted in approximately 1% beta-galactosidase positive cells. Transfer of the ***interleukin*** - ***1*** ***receptor*** ***antagonist*** complementary ***DNA*** resulted in the production of 24 ng/ml/10(6) cells interleukin-1 receptor antagonist protein in 48 hours. CONCLUSIONS: The introduction of exogenous therapeutic genes into cells from the intervertebral end plate opens the possibility for a local gene-based treatment of intervertebral disc degeneration. This approach avoids some of the shortcomings of conventional drug- and surgery-based treatments and has the potential to be specific, effective, and appropriate to the chronicity of the disease.

L7 ANSWER 4 OF 17 MEDLINE
AN 94358479 MEDLINE
DN 94358479
TI Severity of alopecia areata is associated with a polymorphism in the interleukin-1 receptor antagonist gene.
AU Tarlow J K; Clay F E; Cork M J; Blakemore A I; McDonagh A J; Messenger A G; Duff G W
CS Section of Molecular Medicine, University of Sheffield, U.K.
SO JOURNAL OF INVESTIGATIVE DERMATOLOGY, (1994 Sep) 103 (3) 387-90.
Journal code: IHZ. ISSN: 0022-202X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199412
AB One of the most potent pro-inflammatory mediators is the early-acting cytokine interleukin-1. Its actions are regulated by a structurally related anti-inflammatory cytokine known as the ***interleukin*** - ***1*** ***receptor*** ***antagonist***. We have previously characterized a ***DNA*** polymorphism in this gene (IL-1rn) and have found associations between allele 2 and several chronic inflammatory diseases. In the present study, we tested the frequency of allele 2 of the IL-1rn gene in 90 patients with alopecia areata compared with 261 healthy controls. There was a significant association between allele 2 of the polymorphism and the severity of alopecia areata. The frequency of allele 2 increased from 24.1% in the control population to 25.9%

in patchy alopecia areata, 36.1% in alopecia totalis, and 47.2% in alopecia universalis (p = 0.005). This severity association is similar to that found in other epithelial-related diseases, including inflammatory bowel disease, lichen sclerosus, and systemic lupus erythematosus.

L7 ANSWER 5 OF 17 MEDLINE
AN 90136921 MEDLINE
DN 90136921
TI Primary structure and functional expression from complementary ***DNA*** of a human ***interleukin*** - ***1*** ***receptor*** ***antagonist*** .
AU Eisenberg S P; Evans R J; Arend W P; Verderber E; Brewer M T; Hannum C H; Thompson R C
CS Synergen Inc., Boulder, Colorado 80301..
SO NATURE, (1990 Jan 25) 343 (6256) 341-6.
Journal code: NSC. ISSN: 0028-0836.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199005
AB Human monocytes induced with adherent IgG secrete an interleukin-1 receptor antagonist which could be important for the in vivo regulation of IL-1 activity. A complementary DNA for this molecule has been isolated from a human monocyte library. Analysis of monocyte RNA indicates that the gene is transcriptionally regulated. The sequence of the receptor antagonist indicates that it is structurally similar to IL-1 beta. Expression of the cDNA in Escherichia coli yields IL-1 receptor antagonist activity.

L7 ANSWER 6 OF 17 CAPLUS COPYRIGHT 1998 ACS
AN 1998:11628 CAPLUS
DN 128:126881
TI Mouse IL-1 receptor antagonist isoforms: complementary DNA cloning and protein expression of intracellular isoform and tissue distribution of secreted and intracellular IL-1 receptor antagonist in vivo
AU Gabay, Cem; Porter, Brandon; Fantuzzi, Giamila; Arend, William P.
CS Division Rheumatology, Department Medicine, University Colorado Health Sciences Center, Denver, CO, 80262, USA
SO J. Immunol. (1997), 159(12), 5905-5913
CODEN: JOIMA3; ISSN: 0022-1767
PB American Association of Immunologists
DT Journal
LA English
AB IL-1R antagonist (IL-1Ra) is a competitive inhibitor of the binding if IL-1 to IL-1R. IL-1Ra refers to two different proteins derived from the same gene by alternate splicing of two different first exons. One protein contains a leader sequence and is secreted (sIL-1Ra), whereas the other remains intracellular (icIL-1Ra). The authors describe the cloning of mouse icIL-1Ra cDNA, the expression of the recombinant mouse icIL-1Ra protein, and the tissue distribution of sIL-1Ra and icIL-1Ra mRNA and of icIL-1Ra protein in control and LPS-injected mice. As described in the human and the rabbit, mouse icIL-1Ra protein differs from mature mouse sIL-1Ra protein by seven amino acids at the amino terminus. In addn., human and mouse icIL-1Ra are 77% identical. Regulation if IL-1Ra isoforms was examd. in normal mice and after LPS injection. Circulating levels were undetectable in control mice, but were strongly increased 4 h after LPS injection. Using a RNase protection assay (RPA), the authors found that icIL-Ra mRNA was expressed constitutively in skin and in LPS-stimulated RAW 264.7 murine macrophages. Consistent with the RNA studies, Western blot anal. showed that murine icIL-1Ra protein was constitutively expressed in skin and in LPS-stimulated RAW 264.7 cells. In contrast, sIL-1Ra mRNA was not detected by RPA in tissues of control mice, but was strongly up-regulated in the lung, spleen, and liver after LPS injection. Using RPA, primer extension assay and 5' rapid amplification of cDNA ends, the authors were able to demonstrate the presence of different transcription start sites for murine sIL-1Ra mRNA.

L7 ANSWER 7 OF 17 CAPLUS COPYRIGHT 1998 ACS
AN 1997:307955 CAPLUS
DN 126:334259
TI Perifollicular Transgenic Expression of Human Interleukin-1 Receptor Antagonist Protein following Topical Application of Novel Liposome-Plasmid DNA Formulations In Vivo
AU Niemiec, Susan M.; Latta, Jill M.; Ramachandran, Chandrasekharan; Weiner, Norman D.; Roessler, Blake J.
CS College of Pharmacy, University of Michigan, Ann Arbor, MI, 48109-1065, USA
SO J. Pharm. Sci. (1997), 86(6), 701-708
CODEN: JPMSAE; ISSN: 0022-3549
PB American Chemical Society
DT Journal
LA English
OS CJACS-IMAGE; CJACS
AB Expression plasmid ***DNA*** for the human ***interleukin*** - ***1*** ***receptor*** ***antagonist*** (IL-1ra) protein was formulated with nonionic:cationic (NC) liposomes or phosphatidylcholine:cationic (PC) liposomes and applied to the auricular skin of hamsters in single- and multiple-dose protocols. Confocal microscopy identified delivery of plasmid DNA proximal to perifollicular cells, and successful transfection of perifollicular cells was identified by immunohistochem. and ELISA. Skin treated for 3 days with the NC liposomes had statistically significant levels of transgenic IL-1ra present for 5 days post-treatment. Expression of transgenic IL-1ra was specific to areas of skin treated with NC liposomes but not PC liposomes. The results indicate that the NC liposomes can deliver expression plasmid DNA to perifollicular cells and mediate transient transfection in vivo.

L7 ANSWER 8 OF 17 CAPLUS COPYRIGHT 1998 ACS
AN 1996:382905 CAPLUS
DN 125:49306
TI Intracellular isoform of the interleukin-1 receptor antagonist, icIL-1raII, cDNA sequence, and IL-1 production-related pathology diagnosis and treatment
IN Colotta, Francesco; Muzio, Marta; Mantovani, Alberto
PA Applied Research Systems Ars Holding N.V., Neth.
SO PCT Int. Appl., 36 pp.
CODEN: PIXXD2
PI WO 9612022 A1 960425
DS W: AU, BR, BY, CA, CN, EE, FI, JP, KR, KZ, LT, LV, MX, NO, RU, SG, SI, UA
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE
AI WO 95-EP4023 951012
PRAI IT 94-MI2097 941013
DT Patent
LA English
AB The invention describes a new interleukin-1 antagonist active both against IL-1a and IL-1B, a new DNA sequence encoding the IL-1 antagonist and the method for obtaining a IL-1 antagonist by the recombinant DNA technique; the invention also describes the prophylactic, therapeutic and diagnostic use of such new IL-1 antagonist in pathologies deriving from the IL-1 prodn.

L7 ANSWER 9 OF 17 CAPLUS COPYRIGHT 1998 ACS
AN 1996:357169 CAPLUS
DN 125:31946
TI Human interleukin-1 receptor antagonist mutants with enhanced inhibitory activity
IN Boraschi, Diana; Bossu, Paola; Ruggiero, Paolo; Macchia, Giovanni; Tagliabue, Aldo; Frigerio, Francesco; Grifantini, Renata; Frascotti, Gianni; Grandi, Guido
PA Dompe' S.P.A, Italy
SO PCT Int. Appl., 42 pp.
CODEN: PIXXD2
PI WO 9609323 A1 960328
DS W: CA, JP, US
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE
AI WO 95-EP3708 950920
PRAI IT 94-MI1916 940921
DT Patent
LA English
AB DNA mols. that code for IL-1 receptor antagonists with improved biol. activity are described. DNA mols. coding for improved IL-1 receptor antagonists inserted into expression vectors, host cells transformed with the said vectors contg. the DNA coding for improved IL-1 receptor antagonists, and a method for the prodn. of improved IL-1 receptor antagonists (IL-1ra) in essentially pure form are also described. At least one of the amino acid residues in positions 91 and 109 of the sequence of wild-type IL-1ra is replaced by a residue selected from Glu, Arg, Lys, His, and Tyr for position 91, and by a residue selected from Ser, Ala, Phe, Val, Leu, Ile, and Met for position 109. Specifically, 3 mutants were prepd. by std. site-specific mutagenesis procedures: Arg91-IL-1ra, Ala109-IL-1ra, and the double mutant. These mutants possess an enhanced capacity for binding to the both type I and type II IL-1 receptors, so as to provide increased efficacy of inhibition even in pathol. situations where IL-1ra functions little. Prepns. that can be injected or can be administered by some other route, consisting of a pharmaceutical prepn. of the said mutants, are particularly useful as drugs in the field of therapy.

L7 ANSWER 10 OF 17 CAPLUS COPYRIGHT 1998 ACS
AN 1994:453508 CAPLUS
DN 121:53508
TI Immortalized human chondrocytes
IN Goldring, Mary
PA General Hospital Corp., USA
SO PCT Int. Appl., 54 pp.
CODEN: PIXXD2
PI WO 9409118 A1 940428
DS W: JP, US
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE
AI WO 93-US9718 931013
PRAI US 92-959842 921013

DT Patent
LA English
AB In the field of chondrocyte culture and biol. related to using chondrocytes for screening and treatment of cartilaginous diseases, a problem has existed in obtaining immortalized chondrocytes that retain their differentiated characteristics. A method of immortalizing chondrocytes so that they retain their differentiated characteristics and the cells so immortalized are disclosed. Methods of using the cells in gene therapy approaches to cartilaginous disease and methods of using the cells to screen for agents that affect chondrocyte function are disclosed. The use of chondrocytes to produce agents that inhibit vascularization is also disclosed. An immortalized human chondrocyte cell line, C-20/A4, was generated using pMK/SV40 ori- plasmid transfection of juvenile costal chondrocytes. The chondrocytes were characterized.

L7 ANSWER 11 OF 17 CAPLUS COPYRIGHT 1998 ACS
AN 1994:321068 CAPLUS
DN 120:321068
TI Rabbit interleukin-1 receptor antagonist. Cloning, expression, functional characterization, and regulation during intestinal inflammation
AU Cominelli, Fabio; Bortolami, Marina; Pizarro, Theresa T.; Monsacchi, Laura; Ferretti, Maurizio; Brewer, Michael T.; Eisenberg, Stephen P.; Ng, Ray K.
CS Sch. Med., Univ. South. California, Los Angeles, CA, 90033, USA
SO J. Biol. Chem. (1994), 269(9), 6962-71
CODEN: JBCHA3; ISSN: 0021-9258
DT Journal
LA English
AB Genomic and cDNA clones for rabbit interleukin-1 receptor antagonist (IL-1ra) were isolated based on homol. with the human, mouse, and rat IL-1ra gene. A partial genomic clone, obtained by screening a rabbit genomic library, contained coding sequences for the carboxyl-terminal 1-8 amino acids of rabbit IL-1ra. Two classes of cDNA for rabbit IL-1ra were obtained using RNA from inflamed rabbit colon tissue. One class of cDNA coded for a secreted form of IL-1ra, whereas the other coded for a putative intracellular form of rabbit IL-1ra. The latter form is similar to that isolated from human epithelial cells. A partially synthetic rabbit IL-1ra gene was constructed and expressed in Escherichia coli. The recombinant rabbit IL-1ra was purified to homogeneity by ion exchange chromatog. Its affinity was similar to that of human IL-1ra for the human and mouse type I IL-1 receptor. From the cDNA clone and the purified recombinant protein, specific probes were developed for measuring levels of rabbit IL-1ra mRNA and protein in normal and inflamed rabbit tissues. Unlike IL-1.alpha. and IL-1.beta., IL-1ra mRNA and protein were present at detectable levels in normal rabbit colon. During the development of an exptl. formalin-immune complex colitis, rabbit IL-1.alpha. showed a dramatic increase in tissue levels, consistent with previous results; IL-1ra also increased 3-4 fold. Treatment of colitis rabbits with corticosteroids significantly suppressed neutrophil infiltration, IL-1.alpha. levels, but not IL-1ra levels. In contrast, corticosteroid treatment suppressed IL-1ra but not IL-1.alpha. mRNA steady-state levels. The authors' observations demonstrate that IL-1 and IL-1ra synthesis is differentially regulated in healthy and inflamed intestinal tissue.

L7 ANSWER 12 OF 17 CAPLUS COPYRIGHT 1998 ACS
AN 1993:122989 CAPLUS
DN 118:122989
TI Interleukin-1 receptor antagonist protein and analogs containing the interleukin-1 Sclavo peptide
IN Carter, Donald B.
PA Upjohn Co., USA
SO PCT Int. Appl., 30 pp.
CODEN: PIXXD2
PI WO 9117184 A1 911114
DS W: AU, BB, BG, BR, CA, FI, HU, JP, KP, KR, LK, MC, MG, MW, NO, PL, RO, SD, SU, US
RW: AT, BE, BF, BJ, CF, CG, CH, CM, DE, DK, ES, FR, GA, GB, GR, IT, LU, ML, MR, NL, SE, SN, TD, TG
AI WO 91-US2127 910403
PRAI US 90-515468 900427
DT Patent
LA English
AB The interleukin-1 receptor antagonist protein (IRAP) is purified from U937 cells and characterized and analogs prepd. by expression of the corresponding cDNAs in Escherichia coli. The analog is of use in the treatment of arthritis (no data). Induction of IRAP activity in U937 cells by colony-stimulating factors and interleukins was demonstrated and the protein purified chromatog. The protein was shown to be glycosidated and was sequenced and the sequence was used to derive suitable oligonucleotide probes to screen a cDNA bank from phorbol ester-stimulated U937 cells. The cDNA was expressed in E. coli using the trp operon promoter. Analogs of the protein with a nonapeptide replaced by the Sclavo peptide of interleukin 1.beta. were prepd. by expression of a modified cDNA in which the change had been introduced by oligonucleotide-directed site-specific mutagenesis.

L7 ANSWER 13 OF 17 CAPLUS COPYRIGHT 1998 ACS
AN 1992:446282 CAPLUS
DN 117:46282
TI Cloning and expression of murine interleukin-1 receptor antagonist in macrophages stimulated by colony-stimulating factor 1
AU Matsushime, Hitoshi; Roussel, Martine F.; Matsushima, Kouji; Hishinuma, Atsushi; Sherr, Charles J.
CS Dep. Tumor Cell Biol., St. Jude Children's Res. Hosp., Memphis, TN, 38105, USA
SO Blood (1991), 78(3), 616-23
CODEN: BLOOAW; ISSN: 0006-4971
DT Journal
LA English
AB Colony-stimulating factor 1 (CSF-1) can act on mature macrophages to modulate their prodn. of inflammatory cytokines. A cDNA encoding the interleukin-1 receptor antagonist (IL-1Ra) was cloned by subtractive hybridization from a CSF-1-stimulated murine macrophage cell line, sequenced, and expressed in mammalian and bacterial cells. Mouse IL-1Ra is a 22-Kd glycoprotein that is 76% identical to its human counterpart, shows considerably less similarity to IL-1.alpha. and IL-1.beta., and competes with IL-1.alpha. for binding to the type I IL-1 receptor normally expressed on T cells and fibroblasts. CSF-1 treatment of mouse bone marrow-derived macrophages led to a rapid and sustained increase in IL-1Ra mRNA during the G1 phase of the cell cycle as well as to increases in mRNAs encoding IL-1.alpha. and IL-1.beta.. Cycloheximide inhibited CSF-1-induced IL-1.alpha. mRNA synthesis, but augmented IL-1.beta. mRNA prodn. and did not affect induction of IL-1Ra mRNA. No IL-1Ra mRNA was obsd. in CSF-1-stimulated mouse fibroblasts engineered to express CSF-1 receptors, demonstrating that its regulation depends on cell context and can be dissocd. from the proliferative response. In agreement, bacterial lipopolysaccharide, a nonmitogenic activator, also induced IL-1Ra and IL-1 mRNAs in macrophages. Unlike IL-1.alpha. and .beta., IL-1Ra contains a signal peptide. The kinetics of its induction and its ability to gain access to the secretory compartment imply that IL-1Ra may be secreted more efficiently than IL-1, and suggest that macrophages both pos. and neg. regulate the IL-1 response.

L7 ANSWER 14 OF 17 CAPLUS COPYRIGHT 1998 ACS
AN 1992:171936 CAPLUS
DN 116:171936
TI Mouse IL-1 receptor antagonist protein. Molecular characterization, gene mapping, and expression of mRNA in vitro and in vivo
AU Zahedi, Kamyar; Seldin, Michael F.; Rits, Miriam; Ezekowitz, R. Alan B.; Whitehead, Alexander S.
CS Div. Immunol., Child. Hosp., Boston, MA, 02115, USA
SO J. Immunol. (1991), 146(12), 4228-33
CODEN: JOIMA3; ISSN: 0022-1767
DT Journal
LA English
AB The IL-1 receptor (R) antagonist protein (IL-1RN/IL-1rn) is a member of the IL-1 family of inflammatory mediators. The authors have isolated and analyzed a mouse IL-1rn cDNA clone and established that the derived mouse IL-1rn protein sequence is highly homologous to the human counterpart mol. Mouse IL-1rn mRNA may be induced in P388D1 monocytic cells with PMA and in mouse liver in vivo by development of an exptl. inflammation via s.c. injection of azocasein. This latter observation implies the existence of an autocrine hepatic neg. feedback loop that down-regulates the acute phase response and is itself induced at the same time as the major acute-phased proteins. The mouse IL1rn gene was mapped to the proximal region of chromosome 2 between the centromere and spna2; the other known members of the mouse IL-1 gene family, IL1a and IL1b, both map to the same chromosome, although not in close linkage.

L7 ANSWER 15 OF 17 CAPLUS COPYRIGHT 1998 ACS
AN 1992:126536 CAPLUS
DN 116:126536
TI Interleukin 1 receptor antagonist is a member of the interleukin 1 gene family: evolution of a cytokine control mechanism
AU Eisenberg, S. P.; Brewer, M. T.; Verderber, E.; Heimdal, P.; Brandhuber, B. J.; Thompson, R. C.
CS Synergen, Boulder, CO, 80301, USA
SO Proc. Natl. Acad. Sci. U. S. A. (1991), 88(12), 5232-6
CODEN: PNASA6; ISSN: 0027-8424
DT Journal
LA English
AB Interleukin 1 receptor antagonist (IL-1ra) is a protein that binds to the IL-1 receptor and blocks the binding of both IL-1.alpha. and -.beta. without inducing a signal of its own. Human IL-1ra has some sequence identity to human IL-1.beta., but the evolutionary relationship between these proteins has been unclear. It is shown that the genes for human, mouse, and rat IL-1ra are similar to the genes for IL-1.alpha. and IL-1.beta. in intron-exon organization, indicating that gene duplication events were important in the creation of this gene family. Furthermore, anal. of sequence comparisons and mutation rates for IL-1.alpha., IL-1.beta., and

IL-1ra suggests that the duplication giving rise to the IL-1ra gene was an early event in the evolution of the gene family. Comparisons among the mature sequences for IL-1ra, IL-1.alpha., and IL-1.beta. suggest that IL-1ra has a .beta.-stranded structure like IL-1.alpha. and IL-1.beta., consistent with the 3 proteins being related. The N-terminal sequences of IL-1ra appear to be derived from a region of the genome different than those of IL-1.alpha. and IL-1.beta., thus explaining their different modes of biosynthesis and suggesting an explanation for their different biol. activities.

L7 ANSWER 16 OF 17 CAPLUS COPYRIGHT 1998 ACS
AN 1990:550387 CAPLUS
DN 113:150387
TI Purification, cloning, expression and biological characterization of an interleukin-1 receptor antagonist protein
AU Carter, D. B.; Deibel, M. R., Jr.; Dunn, C. J.; Tomich, C. S. C.; Laborde, A. L.; Slightom, J. L.; Berger, A. E.; Bienkowski, M. J.; Sun, F. F.; et al.
CS Dep. Mol. Biol. Res., Upjohn Co., Kalamazoo, MI, 49007, USA
SO Nature (London) (1990), 344(6267), 633-8
CODEN: NATUAS; ISSN: 0028-0836
DT Journal
LA English
AB A human myelomonocytic cell line, U937, produced an interleukin-1 (IL-1) receptor antagonist protein (IRAP) which was purified and partially sequenced. A cDNA coding for IRAP was cloned and sequenced. The mature translation product of the cDNA was expressed in Escherichia coli and was an active competitive inhibitor of the binding of IL-1 to the T-cell/fibroblast form of the IL-1 receptor. Recombinant IRAP specifically inhibited IL-1 bioactivity on T cells and endothelial cells in vitro and was a potent inhibitor of IL-1-induced corticosterone prodn. in vivo.

L7 ANSWER 17 OF 17 CAPLUS COPYRIGHT 1998 ACS
AN 1990:472153 CAPLUS
DN 113:72153
TI Primary structure and functional expression from complementary ***DNA*** of a human ***interleukin*** - ***1*** ***receptor*** ***antagonist***
AU Eisenberg, Stephen P.; Evans, Ron J.; Arend, William P.; Verderber, Evie; Brewer, Michael T.; Hannum, Charles H.; Thompson, Robert C.
CS Synergen Inc., Boulder, CO, 80301, USA
SO Nature (London) (1990), 343(6256), 341-6
CODEN: NATUAS; ISSN: 0028-0836
DT Journal
LA English
AB Human monocytes induced with adherent IgG secrete an interleukin-1 receptor antagonist which could be important for the in vivo regulation of IL-1 activity. A cDNA for this mol. was isolated from a human monocyte library. Anal. of monocyte RNA indicates that the gene is transcriptionally regulated. The sequence of the receptor antagonist indicates that it is structurally similar to IL-1.beta.. Expression of the cDNA in Escherichia coli yields IL-1 receptor antagonist activity.